Schizophrenia

with obsessive compulsive features

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While the obsessive compulsive (OC) phenomena in schizophrenia have been described over the years, the condition has received increasing attention in recent years. The clinical and biological significance of OC symptoms in schizophrenia, however, still remain controversial. Although OC symptoms in schizophrenia were once thought to occur rarely and were associated with more benign clinical courses, recent studies have shown greater prevalence rate and poor outcome. In addition, the OC subgroup of schizophrenia responds poorly to the traditional antipsychotic treatments, but may respond positively to adjunctive anti-OCD regimen according to the emerging clinical evidence.[1] While further systematic studies are needed to explore the clinical neurobiological implications of OC phenomena in patients with schizophrenia, current evidence suggests that these patients require specific symptom assessment and individualized pharmacological and psychotherapeutic treatment interventions for optimal outcome.

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INTRODUCTION

Obsessive compulsive (OC) symptoms in schizophrenia have been described in various forms as a part of the schizophrenic phenomena for over a century. The OC symptoms in patients with schizophrenia may take on varied clinical presentations, such contamination, sexual, religious, aggressive, or somatic themes, with or without accompanying compulsions, such as cleaning, checking, hoarding, repeating, or arranging. Early clinicians, such as Westphal,[2] Kraepelin,[3] Stengel,[4] and Bleuler,[5] considered such OC phenomena as either a prodrome or an integral part of the schizophrenic illness. Unfortunately, there has since been little progress in our understanding of the clinical and neurobiological significance of OC phenomenon in schizophrenia. This was mostly due to the restrictive earlier diagnostic criteria and lack of effective treatment intervention. Over the past decade, however, there have been growing interests in a broad range of psychopathologies in schizophrenia, including OC phenomena, in an attempt to find more clinically meaningful subtyping strategy and to better understand the neurobiological basis of the schizophrenic spectrum disorders. Both the classical (e.g., simple, paranoid, disorganized or hebephrenic, and undifferentiated) and more recent (e.g., positive and negative symptoms) nomenclatures[6] are based on the assumption that schizophrenia is a heterogeneous disorder with diverse clinical phenomena and neurobiological pathogenesis. Further understanding of the OC phenomena may thus enlighten our endeavor to construct more clinically meaningful and neurobiologically relevant subtyping strategy in schizophrenic illness.[7] In this article, we will review the assessment and treatment issues in schizophrenia with OC symptoms.

CLINICAL EVIDENCE

The comorbidity of obsessive compulsive disorder (OCD) and OC symptoms in diverse neuropsychiatric disorders has been well established over the years.[8] These include Tourette syndrome (TS), autism, Sydenham's chorea, trichotillomania, dissociative and eating disorders, and other anxiety disorders with or without an overlap of overvalued ideas and delusional symptoms. However, the relationship between OCD and psychotic disorders has intrigued researchers and challenged practicing clinicians. Westphal[2] in 1878 hypothesized that OC syndrome was a variant or a prodrome of schizophrenia, and Bleuler[5] thought that some patients suffering from chronic obsessional symptoms were in fact schizophrenic. Stengel[4] hypothesized a possible interaction between neurotic OC manifestations and psychotic reactions during the course of the illness as a part of adaptive defense mechanisms. In early studies, Jaherresis[9] and Rosen[10] examined clinical records of a large number of schizophrenia cases and found incidence rates of comorbid OC symptoms to be 1.1 percent and 3.5 percent, respectively, and concluded that the patients with OC schizophrenia tended to have a comparatively benign clinical course and better outcome. These early findings that suggest a low prevalence rate and benign clinical course in patients with OC schizophrenia have been challenged in recent years. Insel and Akiskal[11] proposed that OCD may represent a psychopathological spectrum varying along a continuum of insight, and thus a patient at the severe end of the spectrum may be described as having an obsessive compulsive psychosis. They further postulated that a shift from a neurotic obsession (neurosis) to a psychotic delusion may take place when the resistance to intrusive thoughts is abandoned and insight is lost. Based on this new concept, a number of epidemiological and clinical studies including a nationwide, multicenter Epidemiological Catchment Area (ECA) study found the OCD comorbidity rate in schizophrenia to be 12.2 percent, and 1.3 percent in schizophreniform disorder.[12] A retrospective chart review study by Fenton and McGlashan[13] noted a significantly greater comorbid OC symptom prevalence rate (12.8%) in chronic schizophrenia and that the OC schizophrenic subgroup tended to have worse outcomes in areas of social relationships, employment, psychopathology, and global functioning. They concluded that a persistent OC symptom in schizophrenia may serve as a predictor for a poor outcome. In a prospective study, Berman, et al.,[14] examined 120 community outpatients with DSM-IIIR diagnosed schizophrenia using a structured clinical questionnaire and found a comorbid OC prevalence rate of 15 percent.

✓ Persistent OC symptoms in schizophrenia may serve as a predictor for a poor outcome.

These patients had worse outcomes compared to non-OC schizophrenia. More recently, a large community-based, controlled, prospective, epidemiological study in newly diagnosed patients with psychotic disorders found 10- to 20-percent prevalence rates (10.5% schizophrenia/schizoaffective disorder) for comorbid OCD and OC symptoms.[15] Unlike earlier studies that examined the chronic schizophrenic patients that may increase possibility of sampling subjects with two or more co-existing axis I conditions, this study sampled consecutive first admissions of newly diagnosed schizophrenia and affective disorders with psychosis to a single facility. It used structured clinical interview (SCID)[16] to ascertain the diagnoses of both psychosis and anxiety disorders at more than one point in time. This methodological approach improved the diagnostic reliability and also allowed the determination of the persistence and new onset of comorbid anxiety symptoms over a two-year study period. In addition, examining two sets of anxiety symptoms in across three groups of patients with psychotic disorders enabled the study to address the specificity of comorbid associations and their impact on the clinical course using identical assessments. The findings from the study confirmed a high prevalence rate of comorbid anxiety disorders and symptoms in newly diagnosed schizophrenia and schizoaffective disorders (10.5%). Furthermore, the study demonstrated resolution as well as new onset of the anxiety symptoms and disorders during the 24-month follow-up period. Regarding clinician recognition and treatment of comorbid anxiety symptoms/disorders in schizophrenia, only about 10 percent of patients with comorbid OC symptoms were identified by the clinicians. However, despite low rate of recognition by clinicians, 20 percent or more of these patients received treatment that was appropriate for comorbid anxiety disorders.

While the neurobiology of OCD and schizophrenia has been extensively studied in the past decade, there is lack of controlled study in patients with OC schizophrenia. The research evidence implicates dysfunction of dorsolateral prefrontal cortex circuit in schizophrenia and cortico-striatal-thalamic-cortex in OCD, and both disorders involve predominantly dopaminergic and serotonergic neurotransmitter systems.[17,18] A recent paper that examined the neuroanatomical abnormalities in OCD, schizotypal OCD, and schizophrenia showed a significant gray matter volume reduction suggested that that the schizotypal OCD may be a distinct neuropathological process.[19]

Other investigators have examined the neuropsychological profiles of OC schizophrenia in comparison to OCD and non-OC schizophrenic patients. Many reported greater functional impairments in the OC schizophrenic subgroup,[20–23] while other investigators found no significant difference between the two comparison groups.[24,25] In a demographically matched clinical and neuropsychological study of patients of OC and non-OC schizophrenia, we found significantly worse clinical profiles with more severe negative symptoms and greater prefrontal executive function impairments in the OC schizophrenic subgroup. Such observation supports an earlier report suggesting a direct correlation between the prefrontal impairment with negative psychotic symptoms. However, we found no correlation between the presence of OC symptoms and the severity of positive psychotic symptoms in schizophrenia.[21]

✓ A number of recent treatment studies and anecdotal case reports have shown an adjunctive selective serotonin reuptake inhibitor (SSRI) may be an effective intervention [in OC schizophrenia patients].

Treatment studies. Conventional first-generation antipsychotic medications are generally ineffective in the treatment of patients with OC schizophrenia. However, a number of recent treatment studies and anecdotal case reports have shown an adjunctive selective serotonin reuptake inhibitor (SSRI) may be an effective intervention. Early treatment studies[26–29] observed a marked OC symptom reduction in patients with OC schizophrenia when anti-OCD regimen was added to ongoing antipsychotic medication treatment. More recent clinical and research evidence suggests that while many patients benefit from adjunctive SSRI regimen, it has not been universally effective, and a few case reports suggest worsening of the symptoms.[30,31] In a follow-up longitudinal case study, we found a marked OC symptom reduction and functional improvements as

well as improvements in prefrontal executive functions without significant changes in positive psychotic symptoms in chronic, treatment-refractory OC schizophrenia. Furthermore, clinical and neuropsychological improvements were directly associated with the medication changes in adjunctive anti-OCD regimen. Such a specific OC symptom reduction accompanied by the prefrontal function improvement in response to the adjunctive anti-OCD treatment suggests a distinct underlying OC phenomena neurocircuitry in schizophrenia. In clinical practice, we have observed a broad range of therapeutically effective SSRI dose regimens in treatment of OC schizophrenia for an optimal outcome. We would, however, caution that while many reports of adjunctive SSRI suggest positive outcome, there are also reports of worsening of clinical symptoms with the treatment.[30,31] Furthermore, since the introduction of second generation antipsychotic (SGA) medication there has been emergence of clinical evidence suggesting development of *de novo* or exacerbation of preexisting obsessions and compulsive symptoms in well established schizophrenia.[32–34] Preliminary findings suggest that the new onset OC symptoms may respond to the SSRI treatment.[35,36] While such clinical observations may reflect complex underlying serotonin-dopamininergic interface, further controlled studies are needed to examine the pathogenesis of OC phenomena in schizophrenia.

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CLINICAL CASES

Case 1. A 45-year-old Caucasian man presented with a 27-year history of chronic, undifferentiated schizophrenia, including 16 years of institutionalization. On his last hospital admission, he was agitated, psychotic, and engaged in a number of bizarre, stereotyped behaviors, including repeated face and hand washing, as well as ritualistic drinking and touching of door frames before walking through them. The ritualistic behaviors remained unresponsive to treatment and even worsened despite trials of various neuroleptics, both alone and in combination with the adjunctive lithium, carbamazepine, propanolol, and lorazepam treatment. A neurology consultation, including electroencephalogram (EEG) and brain computed tomography (CT) scan, were unremarkable. Treatment with high-dose chlorpromazine (CPZ) resulted in partial reduction in psychotic symptoms and the patient benefited from its sedating effects. The bizarre rituals, however, persisted, and a trial of fluoxetine was started with gradual dose titration. After two weeks of treatment on 40mg/day, his rituals lessened in frequency and intensity. His self-care skills improved, and he became more responsive to ward routines and to staff attempts to engage him in the treatment milieu. After a year of treatment, fluoxetine was reduced to 20mg/day, resulting in a prompt increase in frequency and intensity of his rituals. Subsequent increase to 60mg/day of fluoxetine for six weeks again brought about significant improvement in impulsive and compulsive behaviors. Patient remained markedly improved during the past two years on CPZ and fluoxetine treatment.

Case 2. A 45-year-old Caucasian man diagnosed of chronic paranoid schizophrenia had his first psychotic decompensation at age 18, with bizarre and persecutory delusions and hallucinations accompanied by impulsive and intrusive behaviors. Since then, he has had multiple hospitalizations treated with a variety of neuroleptics without much improvement. He subsequently developed repetitive behaviors, such as ritualistic touching of objects, repeated dressing and undressing, and frequent checking rituals. Such ritualistic behaviors began several years after the onset of schizophrenic symptoms. Extensive medical and neurological

✓ Preliminary findings suggest that the new onset OC symptoms may respond to the SSRI treatment.

studies including brain CT scan were unremarkable. He was treated with a wide range of antipsychotics in addition to a variety of adjunctive medications. Trials of fluoxetine and clomipramine in conjunction with neuroleptics brought about increased levels of anxiety, restlessness, and agitation. Due to poor treatment response to multiple regimens, he was started on clozapine treatment. Initiation of clozapine treatment rapidly brought about marked increase in agitation and exacerbation of ritualistic behaviors that caused severe patient distress and management challenges. Discontinuation of clozapine resulted in reductions in impulsive and ritualistic behaviors. A subsequent trial of olanzapine with careful dose titration over several weeks resulted in a substantial reduction of ritualistic symptoms and functional improvement.

Case 3. A 35-year-old single Caucasian man was diagnosed at age 12 with undifferentiated schizophrenia consisting of hallucinations and paranoid delusions. Since then he has had several relapses that responded well to antipsychotic medication treatments. During one hospitalization, which was precipitated by acute onset of paranoid delusions, auditory/visual hallucinations, and catatonic behavior, he responded poorly to the antipsychotic and adjunctive medication treatments, remaining markedly psychotic and dysfunctional. He also began to exhibit increasingly bizarre rituals that included repetitive touching of objects, opening and closing of doors, excessive water drinking, including drinking from the toilet upon restriction of water, and forcefully rubbing and injuring his own eyes. His neurological examination and brain CT scan were normal. Clomipramine (CMI) (25mg/day) was subsequently added to ongoing fluphenazine decanoate (50mg/2weeks) and lithium carbonate (1200mg/d), and gradually increased to 50mg/day over two weeks. After four weeks of 50mg/day treatment, his rituals became markedly less frequent and less intense along with improved socialization and participation in therapeutic activities. However, when CMI was further increased to 150mg/day to achieve the recommended therapeutic dose range, he rapidly became restless with impulsive and agitated behaviors. Subsequent dose reduction to 50mg/day once again resulted in symptom relief and functional improvement. The changes in the patient's psychopathological and neuropsychiatric assessments performed during the treatment period reflected the changes in the regimen. He was eventually discharged and remained markedly improved for a follow-up period of two years.

✓ Varied treatment responses in patients with OC schizophrenia may be attributed to the existence of more than one underlying pathogenesis and possible pharmacokinetics.

DISCUSSION

The clinical vignettes illustrate the clinical diversity and varied treatment responses in patients with OC schizophrenia. Such diversity and earlier diagnostic predicaments continue to challenge management of these patients. The first case illustrates a chronic, treatment-refractory OC schizophrenia who responded well to adjunctive SSRI treatment. OC symptom reduction and the functional improvement were associated with adjunctive SSRI treatment and the dose changes. Similar clinical improvements with SSRIs in OC schizophrenia have been reported by clinicians in recent years. However, other investigators found no significant response or poor response to the adjunctive treatment regimen. Case 2 demonstrates schizophrenia with acute OC symptom exacerbation resulting from clozapine treatment and poor response to adjunctive SSRI treatment. Severe impulsivity and ritualistic behaviors often cause severe distress and functional impairment of a patient and challenges the clinical staff. This observation is consistent with the recently emerging clinical findings of worsening or onset of new OC symptoms in patients with schizophrenia on SGA treatment. While few clinical vignettes observed relief of SGA-induced OC symptoms to SSRI treatment, clinical experience indicates variable or minimal response in many patients. However, the patient responded positively to another SGA olanzapine treatment with OC symptom reduction and functional improvement. The patient described in Case 3 showed a marked OC symptom reduction and functional improvement with low dose, sub-therapeutic SSRI treatment but experienced acute symptom exacerbation and functional deterioration with a standard therapeutic SSRI regimen. He improved once again upon returning to a low-dose SSRI regimen.

As exemplified in these case vignettes, the treatment of patients

with OC schizophrenia can be challenging and difficult to predict as their clinical presentations and treatment responses may vary widely. While some patients with OC schizophrenia may show marked clinical improvements, others may have more modest changes or even worsening of the symptom and functioning. These varied treatment responses may be attributed to the existence of more than one underlying pathogenesis and possible pharmacokinetics. Clinicians must consider other factors including other neurological causes, such as neurotoxic effects and infectious causes.[37] All SSRIs competitively inhibit microsomal P450 isoenzymes in the human liver that can substantially increase the antipsychotic blood level.[38,39]

With all of the strengths and limitations of the presently available clinical studies, the following tentative recommendations may be made regarding pharmacotherapy of OC schizophrenia:

1. **Treatment of OC symptoms with an adjunctive anti-OCD medication in schizophrenia should be considered once the patient is otherwise psychiatrically stable on a maintenance antipsychotic regimen.** The use of adjunctive antidepressants in chronic schizophrenia in partial remission appears to be safe, but there is some evidence that administering antidepressant agents in acutely psychotic schizophrenic patients may increase the risk of symptom exacerbation.[1]

2. **The anti-OCD agents should be carefully selected based on the patient's clinical profile, drug pharmacokinetics, and side effect profiles, including potential to induce or exacerbate agitation/akathisia and anticholinergic effects that are common to both SSRIs and SGAs.** Clinicians must carefully monitor for the worsening or onset of the adverse effects as SSRIs may increase blood levels of all antipsychotic medications by as much as 30 percent.[38,39]

3. **Patients receiving clozapine and other atypical antipsychotics as their maintenance treatment should be carefully monitored for new onset or exacerbation of preexisting OC symptoms.** Consideration might be given to switch to another antipsychotic after carefully weighing the benefits derived from the SGA treatment against the morbidity caused by an increase in OC symptoms. If the SGA treatment is to be continued, SSRI treatment intervention with careful monitoring might be considered.

4. **Finally, current evidence indicates that pharmacotherapy should be combined with the cognitive-behavioral psychotherapy for an optimal outcome in treatment of OC schizophrenia.**[40]

✓ If using an SSRI for OC symptoms, clinicians must carefully monitor for the worsening or onset of adverse effects as SSRIs may increase blood levels of all antipsychotic medications by as much as 30 percent.

CONCLUSION

While OC phenomena have long been recognized in schizophrenia, there is still a lack of systematic studies that have examined their clinical and neurobiological significance. Epidemiological and clinical studies show higher prevalence, worse clinical profiles, and greater cognitive impairments in comorbid OC schizophrenia. Current neurobiological research in both schizophrenia and OCD suggest evidence of multisystem pathogenic mechanisms in both disorders. Unfortunately, there is lack of systematic studies that have examined the pathophysiological implications of OC phenomena in schizophrenia.

While adjunctive therapy with anti-OCD medication treatment needs to be further explored, current evidence supports treatment of severe OC schizophrenia with anti-OCD regimen.

In conclusion, management of OC schizophrenia must include careful consideration of the possible pathogenesis and employ prudent individualized pharmacological and psychotherapeutic approaches for optimal outcome. Further controlled studies to validate the clinical implications and neurobiological pathogenesis of OC phenomena within the schizophrenic syndrome are warranted.

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